Application: NDA 21-399
Drug: ZD1839 (IRESSA)

Team Leader Comments and Regulatory Background for the ODAC

These FDA team leader comments provide a regulatory background for ODAC deliberations on the New Drug Application (NDA) for ZD1839 (IRESSA) for NSCLC. Please refer to Dr Cohen's review for details of FDA's findings and analysis of the data. The NDA efficacy results submitted by the sponsor are based on tumor response data, QOL data, and symptom data in NSCLC patients who have no available therapy. These results are intended to fulfill FDA's requirements for *accelerated approval*. In the following paragraphs FDA's requirements for *accelerated approval* and *regular approval* of new drugs are discussed.

Regular approval versus accelerated approval

Regular marketing approval of oncology drugs requires substantial evidence of efficacy from adequate and well-controlled clinical trials. Guidance promulgated in the 1980's indicated that efficacy should be demonstrated by prolongation of life, a better life, or an established surrogate for at least one of these. In 1992 Subpart H was added to the NDA regulations to allow *accelerated approval* (AA) for diseases that are *serious or life-threatening* where the new drug appears to provide *benefit over available therapy*. AA can be granted on the basis of a *surrogate endpoint* that is *reasonably likely to predict clinical benefit.* After AA, the applicant is required to perform a post-marketing study to demonstrate that treatment with the drug is indeed associated with clinical benefit. If the post-marketing study fails to demonstrate clinical benefit or if the applicant does not show *due diligence* in conducting the required study, the regulations describe a process for rapidly removing the drug from the market.

Under AA, tumor response has been used a surrogate *reasonably likely* to predict clinical benefit for nine oncology drug accelerated approvals:

Oncology drug accelerated approvals based on tumor response

Drug	Indication
Liposomal doxorubicin	Kaposi's sarcoma, second line
Docetaxel	Breast cancer, second line
Irinotecan	Colon cancer, second line
Capecitabine	Breast cancer, refractory
Liposomal cytarabine	Lymphomatis meningitis
Temozolomide	Anaplastic astrocytoma, refractory
Liposomal doxorubicin	Ovarian cancer, refractory
Gemtuzumab ozogamicin	AML, second line, elderly
Imatinib mesylate	CML, blast phase, accel. phase & failing interferon

The accelerated approval regulations were first applied to the approval of AIDS drugs. These early AAs used a different model of drug approval than that commonly used in oncology. AA was based on an interim analysis of a surrogate endpoint evaluated in a randomized controlled trial. Subsequent proof of clinical benefit and regular drug approval were usually based on final analyses of the same trial. In contrast, AA in oncology has usually relied on response rate as the surrogate endpoint, usually determined in non-randomized trials with limited patient numbers. Clinical benefit has been demonstrated in randomized trials after drug approval, usually in patients with less refractory tumors.

Although AA has been useful for approving many new anticancer drugs, there are disadvantages to drug development based on non-randomized Phase 2 trials in refractory populations. Once the drug is available, it may be difficult to initiate the required confirmatory RCT in the population for which the drug is approved. The small Phase 2 studies provide only limited safety data, and is often used in a wider population than the one studied.

Evaluation of the ZD1839 data in a regulatory context

As outlined by Dr. Cohen, the applicant's efficacy claim is based on a 10% FDA-verified partial response rate in 139 patients with refractory NSCLC and the applicant's findings of improvements in cancer related symptoms and improvement in quality of life. The ODAC will be asked to advise FDA whether available data are reasonably likely to predict that ZD1839 provides clinical benefit in NSCLC. As discussed below, the ODAC advice to FDA should consider the following points (discussed in the following paragraphs):

1) Is a 10% response rate reasonably likely to predict clinical benefit in refractory NSCLC?

2) What are the meaning of the analyses of tumor symptoms and QOL data in the context of a single arm study?

3) How do we incorporate in our deliberations the reported negative results of two large randomized first-line NSCLC trials of standard chemotherapy plus or minus ZD1839?

Response Rate

Is a 10% response rate in 139 patients sufficient to support AA in refractory NSCLC for a drug that, compared to many cytotoxic anticancer agents, is relatively nontoxic? Low response rates have been predictive of clinical benefit in some settings. Irinotecan received AA in the treatment of refractory colon cancer based on a relatively low response rate and subsequently demonstrated a survival benefit both in the refractory and the first-line settings. Whether a 10% response rate in lung cancer would be reasonably likely to predict clinical benefit, and thus support AA, is a good question for the clinical experts on the ODAC.

Tumor Symptom and QOL data

What are the meaning of the analyses of symptom data and QOL data in the context of a single arm study? The applicant has done a thorough job of evaluating symptomatic changes, but uncertainty regarding the meaning of these data cannot be fully resolved without a concurrent control arm. The applicant claims that clinical benefit is demonstrated in individuals showing a 28-day, 2-point improvement on the 28-point Lung Cancer Subscale (LCS) of the Functional Assessment of Cancer Therapy for Lung Cancer (FACT-L). The 2-point threshold is based on studies showing that a 2-3 point LCS change in study populations is correlated with changes in performance status, weight loss, and TTP. The applicant finds that about 40% of patients in Study 39 derive such benefit, and that the benefit correlates with response and survival. For instance, the rate of a 2-point response on the LCS was 96% for objective tumor responders, 71% for stable disease patients, and 17% for progressors.

There are fundamental problems with the applicant's symptom benefit claims. Without a concurrent control arm, we cannot know whether these symptom findings might not result entirely from placebo effect, from hope associated with starting a promising investigational cancer drug. While a 2-point difference on the LCS determined in study populations may have some meaning in a randomized study, there are no data validating its use as an efficacy endpoint for individuals in a single-arm study. Alternatively, as noted by Dr. Cohen, some symptom improvement could be attributed to concomitant medications given to ameliorate these symptoms. A correlation of positive symptom findings with response rate would not be totally unexpected. One might expect that responders would feel better after being informed of their tumor status. In addition, some analytical bias would be expected, for instance, patients going off study early because of tumor progression might not provide sufficient data for the required 28-day verification of symptom response. Therefore, patients with early objective progression could not have documented symptom responses. Similarly, the 2-point LCS response associations with tumor response and with survival could be from having shared prognostic factors, e.g., prognostic factors (known or unkown) for response, tumor symptom improvement, and survival may be similar. Rather than causing symptom improvement or survival prolongation, tumor response might merely be associated with symptom changes and longer survival through shared baseline prognostic factors.

In the final analysis, it is unclear that the changes observed on the LCS symptom scale represent significant clinical benefit and that the changes observed can be confidently ascribed to ZD1839 treatment. A randomized, blinded trial will be required to make this determination. Although such data might enter into one's judgement whether a 10% response rate is reasonably likely to predict clinical benefit in the refractory NSCLC setting, they clearly are not sufficient for a clinical benefit claim for full NDA approval.

Preliminary results from ZD1839 in first-line treatment of NSCLC

Recently the applicant provided FDA with preliminary analyses of two trials evaluating standard chemotherapy plus or minus ZD1839 in first-line treatment of NSCLC. Despite being adequately powered (about 350 patients per arm) and having adequate follow-up (about 240 events per arm) neither study showed a survival benefit for ZD1339.

Study 14 Survival

	At Risk	Events	Median in Months	1-year
500 mg ZD1839	365	243	9.9	44%
250 mg ZD1839	365	248	9.9	42%
Placebo	363	236	11.1	45%

Study 17 Survival

	At Risk	Events	Median in Months	1-year
500 mg ZD1839	347	246	8.7	38%
250 mg ZD1839	345	232	9.8	42%
Placebo	345	247	9.9	42%

Similarly there was no improvement in response rate:

	Study 14 Response Rate	**Study 17 Response Rate**
500 mg ZD1839	49.7%	32.1%
250 mg ZD1839	50.1%	35.0%
Placebo	44.8%	33.6%

Even though these data were generated in the first-line NSCLC treatment setting, they are important for our determination of ZD1839 efficacy in treating refractory NSCLC. After gaining accelerated approval based on the surrogate endpoint of tumor response in the refractory setting, applicants have often designed clinical trials in first- or second-line treatment settings to demonstrate a survival benefit or some other clinical benefit. The latter evidence has been considered sufficient to convert the drug's status from accelerated to regular approval. The FDA has never received a cancer drug application for accelerated approval when definitive data in another related setting show a lack of efficacy. An important question for the ODAC is how these first-line treatment data affect one's view of whether a 10% response rate in the refractory setting is reasonably likely to predict clinical benefit.

If after viewing these data the ODAC does not find that the 10% response rate in Study 039 is reasonably likely to predict clinical benefit in NSCLC, then the FDA will consider this a recommendation against accelerated approval of ZD1839. The FDA will then seek advice on the expanded access program for ZD1839. Many thousands of patients have received ZD1839 through expanded access, and the impact of the results from first-line trials in NSLC on the expanded access program needs to be discussed.

We look forward to discussion of these matters before the ODAC.

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